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EXAMINER	
GUNTER, DAVID R	

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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/933,307	RAMBERG, ELLIOT R.	
	Examiner	Art Unit	
	David R. Gunter	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 and 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Objections

1. Claims 1, 2, 7, and 8 are objected to because of the following informalities: each of these claims contain multiple method steps. In some cases, the method steps are separated by commas (after 1 a and c), and in other cases they are separated by semicolons (after 1 b and d). Either the use of commas or semicolons is acceptable, but the same punctuation should be used throughout the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-12 are indefinite because the recitation in claims 1 and 7 of "converting the first proenzyme into an active second enzyme" is unclear. It is not clear how the first proenzyme is converted into an active second enzyme, and how this conversion is related to the first enzyme or the immobilized target analyte. The claims are further indefinite because the lack of a recited relationship between the immobilized analyte and conversion of the first proenzyme into an active second enzyme makes it unclear how the

method accomplishes the stated objective of detecting the target analyte (claim 1) or signal amplification (claim 7).

b. Claims 5 and 11 are indefinite because the meaning of "a nucleic acid sequence, a protein, a peptide, or a single nucleotide polymorphism, or a carbohydrate" is unclear. The repated use of the word "or" in the list of analytes makes it unclear whether the analyte is recited to comprise a single type of molecule or whether "single nucleotide polymorphism" is meant to be recited as part of a group with either "peptide" or "carbohydrate."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-3, 5, 7-9, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Harris, USPN 4,463,090, filed September 30, 1981, issued July 31, 1984 (hereinafter "Harris").

a. Claim 1 of the instant application recites a method for detecting a target analyte, comprising, (a) attaching a reporter molecule to an immobilized target analyte, wherein the reporter molecule comprises a first enzyme, (b) adding a composition comprising a first proenzyme, (c) converting the first proenzyme into an active second enzyme, (d) adding a composition comprising at least one substrate of the active second enzyme, and (e) detecting the change in the substrate due to activity of the active second enzyme.

Harris teaches a method for detecting a target analyte identical to that of the instant application. A target analyte is immobilized by bringing the target analyte into contact with an antibody that is specific to the analyte and which is covanlently linked to a solid support. A second analyte-specific antibody which is conjugated to an enzymatic reporter molecule binds to the immobilized analyte, thereby attaching the reporter to the immobilized target analyte (Harris, column 7, lines 4-17). A first proenzyme is added, and is converted by the reporter molecule into a second enzyme (column 3, diagram in center of column; also column 7, lines 24-28). A substrate of the active second enzyme is added, and the change in the substrate due to the activity of the active second enzyme is detected (column 7, lines 38-42).

b. Regarding claim 2, Harris teaches the embodiment in which the method further comprises adding a second proenzyme after step (b), wherein the second proenzyme is changed to an active third enzyme by the activity of the second enzyme (diagram, top of column 4; column 7, lines 42-50).

c. Regarding claim 3, Harris teaches the embodiment in which the converting of the first proenzyme into an active second enzyme comprises cleavage of the first proenzyme into an active second enzyme and at least one other peptide by the active first enzyme. Harris teaches multiple specific examples in columns 9 and 10 including the cleavage of trypsinogen to form trypsin (diagram, column 9, line 50), and cleavage of chymotrypsinogen to form chymotrypsin (diagram column 9, line 62).

d. Regarding claim 5, Harris teaches the embodiment in which the target analyte is a protein (column 5, lines 58-60).

e. Regarding claim 7, the claim recites a method of signal amplification, comprising, (a) hybridizing a reporter molecule to an immobilized target analyte, wherein the reporter molecule comprises a first enzyme, (b) adding a composition comprising a first proenzyme, (c) converting the first proenzyme into an active second enzyme, (d) adding a composition comprising at least one substrate of the active second enzyme, and (e) detecting the change in the substrate due to activity of the active second enzyme.

Harris teaches a method of signal amplification identical to that of the instant application. A target analyte is immobilized by bringing the target analyte into contact with an antibody that is specific to the analyte and which is covanlently linked to a solid support. A second analyte-specific antibody which is conjugated to an enzymatic reporter molecule binds to the immobilized analyte, thereby hybridizing the enzyme to the immobilized target analyte (Harris, column 7, lines 4-17). A first proenzyme is added, and is converted by the reporter molecule into a second enzyme (column 3, diagram in center of column; also column 7, lines 24-28). A substrate of the active second enzyme is added, and the change in the substrate due to the activity of the active second enzyme is detected (column 7, lines 38-42).

f. Regarding claim 8, Harris teaches the embodiment in which the method further comprises adding a second proenzyme after step (b), wherein the second proenzyme is changed to an active third enzyme by the activity of the second enzyme (diagram, top of column 4; column 7, lines 42-50).

g. Regarding claim 9, Harris teaches the embodiment in which the converting of the first proenzyme into an active second enzyme comprises cleavage of the first proenzyme

into an active second enzyme and at least one other peptide by the active first enzyme. Harris teaches multiple specific examples in columns 9 and 10 including the cleavage of trypsinogen to form trypsin (digram, column 9, line 50), and cleavage of chymotrypsinogen to form chymotrypsin (diagram column 9, line 62).

h. Regarding claim 11, Harris teaches the embodiment in which the target analyte is a protein (column 5, lines 58-60).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claim 4 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris in view of Berne and Levy (eds.), Physiology, second edition, published by The C.V. Mosby Company, 1988 (hereinafter "Berne and Levy"). Harris teaches a method for detecting a target analyte and for signal amplification identical to those of the instant application. A target analyte is immobilized by bringing the target analyte into contact with an antibody that is specific to the analyte and which is covanlently linked to a solid support. A second analyte-specific antibody which is conjugated to an enzymatic reporter molecule binds to the immobilized analyte, thereby attaching the reporter to the immobilized target analyte (Harris, column 7, lines 4-17). A first proenzyme is added, and is converted by the reporter molecule into a second enzyme (column 3, diagram in center of column; also column 7, lines 24-28). A substrate of the active second

enzyme is added, and the change in the substrate due to the activity of the active second enzyme is detected (column 7, lines 38-42).

Claims 4 and 10 recites the additional limitation to claim 3 and 9, respectively, that the detecting step comprises detection of the "at least one other peptide" generated when the first proenzyme is cleaved to form an active second enzyme. Harris teaches detection of the activity of the enzyme, but does not teach detection of the cleaved fragment of the proenzyme.

However, it was well known by those of ordinary skill in the art at the time the application was filed that activation of the proeznymes trypsinogen and chymotrypsinogen taught by Harris (diagrams, column 9 and 10) requires the cleavage of the proenzyme to form an active enzyme and an another peptide (Berne and Levy, page 721, right column, last paragraph; also figure 44-5, page 722). The detection of trypsin or chymotrypsin activity taught by Harris (column 7, lines 38-42) can only take place if these enzymes are active, and the enzymes can only be active if the proenzymes have been cleaved to form the active enzyme and another peptide. Therefore, it would have been obvious to one of ordinary skill in the art that an assay of trypsin or chymotrypsin activity will also function as an assay for the detection of the other peptide.

5. Claims 6 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller in view of Burnham, et al., USPN 5,486,459, filed January 30, 1995, issued January 23, 1996 (hereinafter "Burnham"). Harris teaches a method for detecting a target analyte and for signal amplification identical to those of the instant application. A target analyte is immobilized by bringing the target analyte into contact with an antibody that is specific to the analyte and which

is covanlently linked to a solid support. A second analyte-specific antibody which is conjugated to an enzymatic reporter molecule binds to the immobilized analyte, thereby attaching the reporter to the immobilized target analyte (Harris, column 7, lines 4-17). A first proenzyme is added, and is converted by the reporter molecule into a second enzyme (column 3, diagram in center of column; also column 7, lines 24-28). A substrate of the active second enzyme is added, and the change in the substrate due to the activity of the active second enzyme is detected (column 7, lines 38-42).

Claims 6 and 12 recite the additional limitation to claim 1 and 7, respectively, that the compositions comprising at least one substrate comprises proteins of the complement system. Harris teaches the use of substrates from a variety of biological systems including digestive enzymes (typsinogen, chymotrypsinogen), blood clotting factors (prothrombin, Factor XII), and components of the rennin-angiotensin system (angiotensinogen, angiotensin 1; see table 1, and the diagrams in columns 5, 9, 10, and 11). Harris does not specifically teach the use of proteins of the complement system.

Burnham, however, teaches a method of detecting enzyme activity using "an enzyme amplification system such as fibrin/coagulation cascade, a complement cascade, a trypsin/trypsinogen cascade, or a combination thereof" (column 4, lines 15-18). Furthermore, Burnham teaches that proteins of the complement cascade "are linearly or logarithmically amplified upon incubation with substrate, thereby producing a rapid build-up of enzyme modified substrate, or product, which is easily detected" (Burnham, column 4, lines 18-21). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Harris to include proteins of the complement system because of their well-

studied properties, the ready availability of commercially prepared kits and reagents for their detection, and the rapid and easily detectable accumulation of modified substrate.

Conclusion

6. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David R. Gunter whose telephone number is (703) 308-1701. The examiner can normally be reached on 9:00 - 5:00 M - F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-9212 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.

David R. Gunter, DVM, PhD
November 26, 2002

GARY JONES
SUPERVISORY PATENT EXAMINER